

### Diarrhea

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Few medical conditions are more common than diarrhea, clinically noted as increased quantity or frequency of stool and an associated decrease in solid consistency. Almost all patients will experience diarrhea at some point. Although most of those cases will not require a physician's attention, diarrhea is a significant source of medical morbidity, mortality, and substantial economic expense.

Clinically, diarrhea can be diagnosed in the presence of (1) more than three loose watery stools per day or (2) a significant increase in frequency or decrease in consistency from the patient's baseline bowel function.

Diarrhea can be classified as acute (up to 2 weeks), persistent (2 to 4 weeks), or chronic (greater than 4 weeks). In some instances, diarrhea may last indefinitely, for example in IBS with diarrhea.

Diarrhea is a nonspecific physiologic response that can reflect a variety of underlying etiologies both infectious and noninfectious. The vast majority of infectious cases of diarrhea are secondary to viral disease. A smaller number can be related to bacterial and parasitic infections. Among noninfectious causes of diarrhea, malabsorption and medications are two leading and medically important considerations.

### VIRAL GASTROENTERITIS

The vast majority of all cases of diarrhea in the United States can be attributed to viral infection and present a considerable medical and economic challenge. Viral etiologies (most prominently norovirus) are responsible for more than 90% of all gastroenteritis (GE) outbreaks reported to the CDC. Viral GE represents the second most common illness reported among family units in the United States. Although generally self-limited and generally not fatal among immunocompetent adults, viral GE is responsible for approximately 100,000 hospitalizations annually in the United States as well as several hundred deaths. Worldwide viral GE is responsible for 800,000 deaths annually primarily due to dehydration and electrolyte depletion.

The vast majority of all viral GE can be attributed to one of four viral agents: norovirus, rotavirus, enteric adenovirus, or astrovirus. Of these rotavirus and norovirus are by far the most common.

**Table 18-1. Endemic versus Epidemic Viral Gastroenteritis**

	ENDEMIC	EPIDEMIC
Etiology	Group A rotavirus	Norovirus
Age range affected	4 to 24 months	5 years and up
Peak season (United States)	December through April	Small peak in winter
Transmission	Fecal-oral	Foodborne, fecal-oral
Source or location	Variable but seen within families; community-acquired infection has been reported	Restaurants, hospitals/long-term care facilities, daycare/schools, vacation areas (including cruise ships)

Viral GE can be epidemiologically distinguished as either endemic or epidemic (Table 18-1). Epidemic GE is characterized by distinct outbreaks usually associated with the introduction of the virus into a defined population such as restaurant patrons, long-term care facility residents, or cruise ship passengers. In general epidemic viral GE does not affect young children (<24 months). Although epidemic viral GE shows a small peak in the winter, seasonality is not usually a prominent feature. Most epidemic viral GE is caused by norovirus.

Endemic viral GE is generally characterized by person-to-person infection that may be primary, reinfection, or community acquired. There is distinct seasonality to endemic viral GE with a peak from December through April in the United States. Most cases are caused by rotavirus and most symptomatic illness is confined to young children 4 to 24 months old. Enteric adenovirus and astrovirus are the less common causes of endemic GE.



## ROTAVIRUS

- Leading cause of viral GE worldwide
- Fecal-oral transmission
- Incubation generally less than 48 hours
- Fecal shedding for 10 to 21 days
- Within affected families 50% of exposed children and up to 30% of exposed adults will become infected.
- Peaks December through April in United States; spreads from southwest to northeast



## NOROVIRUS

- 90% of adults are seropositive
- Only limited immunity associated with seropositivity
- Responsible for two thirds of all foodborne illness
- Fecal-oral transmission
- Incubation 24 to 48 hours
- Fecal shedding 2 to 3 weeks
- Resistant to heating up to 60° C and to chlorine disinfectant



## ENTERIC ADENOVIRUS

- Responsible for 3% to 10% of endemic GE in patients less than 2 years old
- Incubation period is 8 to 10 days



## ASTROVIRUS

- Responsible for up to 9% of endemic pediatric GE worldwide
- Responsible for up to 7% of daycare center GE
- Responsible for approximately 10% of diarrhea in patients with AIDS

### Symptoms

- Frequent loose stools, more than three per day ++++
- Decreased stool consistency ++++
- Vomiting ++++
- Fever is variably present +++
- Bloody stool +

### Signs

- Related to dehydration secondary to GI fluid loss
- Frequency is directly related to the degree of dehydration
- Tachycardia
- Skin changes
- Dry mucous membranes
- Hypotension
- Sunken fontanelles (infants)

### Comments and Treatment Considerations

Although viral GE is more common than bacterial diarrhea, patient consideration should be given to possible bacterial or parasitic etiologies. Primary evaluation consists of a careful history to identify critical symptoms suggestive of nonviral disease including severity of diarrhea (more than four stools per day for >3 days), blood, limited vomiting, and prolonged incubation periods. The Kaplan criteria

**Table 18-2. Kaplan Criteria for Viral Gastroenteritis**

- More than 50% of patients experience vomiting
- Mean incubation period 24 to 48 hours
- Mean duration is 12 to 60 hours
- All bacterial cultures are negative

(Table 18-2) have been used to distinguish clinically between viral and bacterial etiologies during outbreaks of diarrhea. The Kaplan criteria have been shown to be 99% specific and 68% sensitive for identifying viral causes of GE.

Serum antibody testing is not generally useful for suspected cases of rotavirus (endemic GE). Greater than 90% of adults demonstrate antibodies. Antibody presence does not confer long-term immunity. In patients with more than four stools per day for more than 3 days' duration, bacterial cultures will be positive in approximately 90% of cases. Visibly bloody diarrhea will demonstrate positive bacterial cultures in approximately 20% of cases.

In critically ill patients with impending or evident organ failure, emergent management is required. In noncritically ill patients, treatment for viral GE is largely directed toward fluid and electrolyte repletion. Oral rehydration therapy (ORT) has been shown to be as effective as IV rehydration in most patients with GE-associated dehydration. ORT for mild (3% to 5% body weight loss) to moderate (6% to 9% body weight loss) dehydration can be used alone for patients who can tolerate oral fluids. IV hydration with or without oral rehydration therapy is recommended for patients with severe dehydration.

## BACTERIAL AND PARASITIC INFECTION

Although less common than viral GE, bacterial and parasitic GE remains a medically and economically important source of concern. While there are no well-established criteria for the diagnostic consideration of bacterial or parasitic diarrhea, several key clinical findings should prompt evaluation including fever, blood, severity, or persistence of diarrhea. In addition a history of recent travel, known exposure, or antibiotic use should also prompt consideration of bacterial or parasitic infection (Table 18-3).

**Table 18-3. Factors Favoring Bacterial or Parasitic Etiology for Diarrhea**

- Marked fever
- Visibly bloody diarrhea or report of bloody diarrhea
- Severe diarrhea defined as more than four stools per day for >3 days
- Persistent (>14 days' duration) or chronic diarrhea (>1 month's duration)
- Recent antibiotic use
- Recent hospitalization
- Recent travel



## BACTERIAL INFECTION

The estimated prevalence of bacterial diarrhea, however, is 5% to 7% of all diarrhea cases. Among the bacterial causes of diarrhea a handful of organisms represent the most commonly cultured bacteria. One large study in the early 1990s found positive bacterial cultures in 5.6% of samples. The four most common organisms were *Campylobacter* (2.3%), salmonella (1.8%), shigella (1.1%), and *Escherichia coli* 0157:H7 (0.4%). Of note in this study, *E. coli* was found in 7.8% of samples reporting blood and only 0.1% of those not reporting blood. A second large study released in 2005 found similar prevalent organisms but also noted the presence of cryptosporidium at rates in excess of *E. coli*. Less common organisms noted in this study included yersinia, listeria, vibrio, and cyclospora.

Bacterial diarrhea can be usefully categorized as primarily originating in either the small or large bowel.

*Clostridium difficile* infection results in diarrhea associated with colitis and is usually the result of antibiotic use. The bacterial causes of diarrhea are reviewed under "Medication-Related Diarrhea."

### Campylobacter

- Primary source is undercooked infected poultry
- Second leading cause of foodborne illness in the United States
- Incubation period is 3 days (1 to 7 days)
- Prodromal fever often noted +++; abdominal pain more prominent than in most diarrheas; nausea is common +++/++++ but vomiting is less common ++ (≈15%)
- Associated with a watery and/or hemorrhagic diarrhea, large bowel disease ++++/++++
- Usually self-limited (≈7days) but abdominal pain may persist
- Bacterial shedding persists for approximately 1 month (mean 38 days) but is not clinically important.
- Does not usually require antibiotic therapy but is sensitive to macrolides and fluoroquinolones orally or aminoglycosides parenterally
- Has been associated clinically with reactive arthritis and Guillain-Barré disease

### Salmonella

- Non-typhoidal salmonella is the leading cause of foodborne illness.
- Most commonly associated with poultry, eggs, and milk; also found in fresh produce, meats, and pets (notably reptiles)
- Peak incidence in summer and early fall
- Usually presents as small bowel diarrhea (nausea, fever, diarrhea)
- Presentation of salmonella infection may range from asymptomatic to life threatening; patients presenting for evaluation will almost universally present with some combination of nausea, fever, and diarrhea ++++

- Symptoms usually appear 6 to 72 hours after ingestion.
- Antibiotics show little benefit in otherwise healthy adults or children older than 12 months of age.
- Possible indications for antibiotic use in adults include high fever, need for hospitalization, or more than 10 stools per day.
- In infants younger than 3 months of age, antibiotic therapy is recommended to reduce the risk of complications. Some authorities recommend treating all children younger than 1 year of age.
- Treatment is also recommended regardless of age for immunocompromised individuals including sickle cell disease, AIDS, organ transplant, or vascular/osseous prostheses.
- When indicated, antibiotic choice includes third-generation cephalosporins and fluoroquinolones.

## Shigella

- Associated with person-to-person transmission and through contact with contaminated food or water
- Produces classic large bowel diarrhea characterized by small volume bloody +++ (30% to 50%) or mucoid diarrhea ++++ (70% to 85%), associated with high fever ++ (30% to 40%) and abdominal pain ++++ (70% to 90%)
- Disease is self-limited (mean duration  $\approx$  7 days) and does not generally require antibiotics for resolution
- Bacterial shedding persists up to 6 weeks without antibiotic treatment.
- Many experts recommend antibiotic treatment to reduce the risk of person-to-person transmission.
- In general, treatment for suspected shigella may be held until culture results are available. For high-risk patients with suggestive clinical presentations, therapy may be considered prior to culture results. At-risk populations include health care workers, food service workers, older adults, malnourished, daycare center participants, and patients with HIV with or without AIDS.

## *E. coli* 0157:H7

- Foodborne diarrhea associated primarily with undercooked ground beef. Has also been associated with other food sources including unpasteurized apple cider.
- Incubation period between exposure and disease is 3 to 4 days.
- Clinical disease is often characterized by bloody diarrhea (by history or visibly bloody sample), elevated white count ( $>10,000$ ), significant abdominal tenderness and absence of fever. +++ In one study at least three of these five signs/symptoms were present in 65% of all cases of *E. coli*. By contrast at least three were noted in only 19% of cases of shigella, campylobacter, or salmonella.
- The peak incidence of disease in the United States is summer with two thirds of all cases reported in June and September.
- *E. coli* 0157:H7 has been associated with hemolytic-uremic syndrome and thrombocytopenic purpura.



## PARASITIC INFECTIONS

Parasitic infections may also present clinically with diarrhea. Although generally less common and less clinically significant than either viral or bacterial etiologies within the United States, parasitic infections remain a consideration in patients with diarrhea. Worldwide parasitic infections continue to represent a substantial public health and economic challenge.

Although the number of parasites that may present with GI symptoms is large, the most significant organisms are reviewed below. Parasitic infections resulting in diarrhea may be either foodborne or may arise via exposure to infected individuals or contaminated water supplies.

### **Cryptosporidium**

- Intracellular protozoa that reproduce within epithelial cells of the GI tract
- Most common parasitic cause of foodborne illness
- Organism is acquired via contact with contaminated food or water (drinking or swimming) or via contact with another affected individual via fecal-oral transmission
- Associated with diarrhea and biliary disease
- In immunocompetent individuals, cryptosporidial disease is associated with diarrhea and dehydration (at times severe) but is generally self-limited.
- In immunocompromised individuals, cryptosporidial disease may be both more severe and more prolonged.
- Diagnosis is via identification of oocysts on microscopic examination of suspected stool sample.

### ***Giardia lamblia***

- Giardiasis is the second most common parasitic infection in the United States.
- 2.5 million cases annually
- Animals provide the reservoir and transmission is via the fecal-oral route often from exposure to contaminated water supplies.
- Up to 60% of infected adults remain asymptomatic.
- Symptoms include dyspepsia and typical small bowel diarrhea with associated nausea ++++ (70%), vomiting ++ (30%), cramping ++++ (70%), and weight loss +++ (65%).
- Additional symptoms include steatorrhea/foul-smelling stool ++++ (70%), malaise ++++ (85%), and flatulence ++++ (75%).
- Clinical course is marked by a gradual onset and a prolonged duration (2 to 4 weeks).
- Diagnosis is via stool studies for ova and parasites from three separate samples (85% to 90% sensitive).
- Alternative diagnostic options include antibody studies via ELISA or immunofluorescence (90% to 99% sensitive, 95% to 100% specific).
- Treatment is generally with metronidazole and is outlined in [Table 18-4](#).

**Table 18-4. Antibiotic Treatment for Bacterial and Parasitic Gastroenteritis**

ORGANISM	TREATMENT
Campylobacter	5 days of treatment with: <ul style="list-style-type: none"> <li>• Macrolides (e.g., erythromycin 500 mg PO bid)</li> <li>• Aminoglycosides for severe infection</li> </ul>
Salmonella	3 to 7 days of treatment with: <ul style="list-style-type: none"> <li>• Third-generation cephalosporins (e.g., ceftriaxone 2 g IV every day)</li> <li>• Fluoroquinolones (e.g., ofloxacin 400 mg PO bid)</li> <li>• Alternatives include amoxicillin, TMP-SMX</li> </ul>
Shigella	5 days of treatment with: <ul style="list-style-type: none"> <li>• Quinolones (e.g., ciprofloxacin 500 mg PO bid; 1 g PO single-dose therapy is an alternative for mild disease)</li> <li>• Alternative treatments include macrolides and TMP-SMX in patient isolates shown to be sensitive</li> </ul>
<i>E. coli</i> 0157:H7	Supportive therapy only. No proven or generally accepted benefit from antibiotic therapy. In patients with hemolytic-uremic syndrome management should be directed to these sequelae of infection.
Cryptosporidium	Treatment in immunocompetent adults is not usually necessary. When indicated (for persistent symptoms), however, may be treated with: <ul style="list-style-type: none"> <li>• Nitazoxanide, 500 mg PO bid for 3 days</li> </ul> Treatment is generally recommended for children with: <ul style="list-style-type: none"> <li>• Nitazoxanide 100 mg PO bid for 3 days (age 1-3 years old)</li> <li>• Nitazoxanide 200 mg PO bid for 3 days (age 4-11 years old)</li> <li>• 12 years and older as adults</li> </ul> Treatment for immunodeficient individuals has shown variable benefit. Recommended treatment is with: <ul style="list-style-type: none"> <li>• Nitazoxanide 1000 mg bid PO for 2 weeks alone or with azithromycin</li> </ul>
<i>Giardia lamblia</i>	Treatment varies by age and pregnancy status. <ul style="list-style-type: none"> <li>• Nonpregnant adults: metronidazole 250 mg PO tid for 5 to 6 days</li> <li>• Pregnant with mild disease: defer</li> <li>• Pregnant with severe disease: metronidazole as above or paromomycin 500 mg PO qid for 7 to 10 days</li> <li>• Children: albendazole 400 mg PO for 5 days</li> </ul>

**Table 18-4. Antibiotic Treatment for Bacterial and Parasitic Gastroenteritis—cont'd**

ORGANISM	TREATMENT
<i>Entamoeba histolytica</i>	<p>Intestinal disease should be treated for luminal and tissue organisms</p> <p>Luminal disease:</p> <ul style="list-style-type: none"> <li>• Iodoquinol 650 mg PO tid for 20 days <i>or</i></li> <li>• Paromomycin 500 mg PO tid for seven days <i>or</i></li> <li>• Diloxanide furoate 500 mg PO tid for 10 days</li> </ul> <p>Tissue disease:</p> <ul style="list-style-type: none"> <li>• Metronidazole 750 mg PO tid for 10 days</li> </ul>

***Entamoeba histolytica***

- Protozoa transmitted via fecal-oral route
- 10% of the worldwide population infected, primarily in underdeveloped areas
- 90% of infected patients are asymptomatic
- Responsible for approximately 60 million symptomatic infections and 100,000 deaths annually
- Diagnosis is via stool antigen studies that are 87% sensitive and 90% specific.
- Treatment is dependent on the location of infection (intestinal or liver) and is summarized in [Table 18-4](#).

**Cyclospora**

- Usually a foodborne pathogen
- Generally presents with small bowel diarrheal symptoms
- Often associated with severe fatigue and malaise as well as diarrhea
- Course may be prolonged (>3 weeks)

**Symptoms**

- Small bowel disease—High-volume, high-frequency, watery diarrhea with gas, bloating, cramping, and nausea. Generally not associated with reports of bloody diarrhea.
- Large bowel disease—Small-volume, lower-frequency diarrhea with blood or mucus

**Signs**

- Fever
- Abdominal tenderness
- Visible blood
- Hyperactive bowel sounds

**Comments and Treatment Considerations**

- Most cases of bacterial GE do not require antibiotic treatment.
- The cornerstone of treatment for bacterial GE is fluid and electrolyte repletion.

- It is generally not cost-effective, or necessary, to send stool cultures on healthy patients with diarrhea because the vast majority are self-limited without specific treatment. When cultures indicate a specific bacterial etiology and the clinical conditions suggest a need for antibiotic treatment, therapy should begin with antibiotics known to be active against the identified organism. Specific treatment recommendations are highlighted in [Table 18-4](#).



## CHRONIC DIARRHEA

Although often unpleasant and possibly medically concerning, most diarrhea is relatively brief in duration lasting no longer than a few days to a few weeks. In some instances, however, diarrhea may persist beyond 2 weeks (persistent diarrhea) or even beyond a month (chronic diarrhea). When diarrhea has persisted beyond a relatively brief period, physicians should entertain the possibility of either medication-related diarrhea or a malabsorptive process.

Chronic diarrhea may result from a variety of medical conditions including IBS, functional diarrhea, IBD, systemic disease such as thyrotoxicosis or carcinoid syndrome, and malabsorption syndromes. Although a variety of conditions may be associated with malabsorption, the most common disease processes include chronic pancreatitis, celiac disease, lactose intolerance, and bacterial overgrowth. It should be noted that some infectious etiologies may be associated with chronic diarrhea. In cases of chronic diarrhea, a thorough evaluation including stool cultures for bacteria and ova or parasites may be helpful. The most significant of these are covered earlier.

## MALABSORPTION

Malabsorption is defined as dysfunction of nutrient absorption either due to intrinsic GI disease or acquired defects. Although a generally accepted algorithm for evaluation of chronic diarrhea has not been established, the majority of cases ( $\approx 90\%$ ) eventually yield a specific diagnosis.

History should emphasize the nature, frequency, and duration of diarrhea. Risk factors for HIV should be reviewed. Family history should be reviewed for GI disease processes. Additional non-GI symptoms should be reviewed because patterns may be suggestive of specific disease entities.

Travel, exposures, and occupation should be reviewed. Psychosocial stressors should be identified. All chronic and recent acute medical conditions should be identified as well as any medication use associated with these conditions.

### Symptoms

- Symptoms may vary from nearly asymptomatic to fulminant.
- A diagnosis of malabsorption should be prompted by duration of diarrhea because specific symptoms are highly variable in frequency and intensity.

- Classic symptoms include diarrhea, gas, bloating, crampy abdominal pain, flatulence, and excessive bowel noise.
- Patients who present with symptoms consistent with a nutrient deficiency should be evaluated for malabsorption.
- Foul-smelling or greasy-appearing stool
- Weight loss
- Fecal incontinence

### Signs

- The physical examination is rarely revealing in patients with chronic diarrhea.
- Note should be made of fever, rash, ulcers, abdominal distention or tenderness, adenopathy, and thyroid size

### Comments and Treatment Considerations

Additional testing should be largely directed by the history and physical examination because no generally accepted set of tests can be recommended for all patients with chronic diarrhea.

Evaluation for most patients will include a CBC, thyroid function testing, basic electrolyte levels, serum protein or albumin and fecal occult blood testing. In patients for whom infectious etiologies are considered stool samples for white blood cells, ova and parasite and culture may be appropriate. For patients with suspected malabsorption, fecal fat studies may be indicated. In selected patients endoscopic evaluation may contribute to diagnosis.

Treatment is generally directed toward modification of the underlying disease process or avoidance of the inciting agent (e.g., dairy products in lactose intolerance).

## MEDICATION-RELATED DIARRHEA



### MEDICATIONS

Almost any medication may be associated with diarrhea although a few such as metformin and the macrolides have classically been noted to produce diarrhea as a side effect of therapy. A comprehensive review of the patients' medications is warranted in patients who present with chronic diarrhea, who do not manifest other signs or symptoms of infection, or who note an acute change in GI function shortly after initiating a new medication or changing the dose of a previously prescribed medication. In addition to reviewing the timing and nature of the patients' symptoms a review of medication allergies, prior medication reactions, and past or family history of drug sensitivity (such as G6PD deficiency) may help illuminate the connection between medications and diarrhea. In reviewing medications, physicians should take particular care to review possible drug-drug interactions, especially in patients with extensive medication lists.

## Symptoms

- Diarrhea with or without additional GI symptoms shortly after medication change or initiation
- Absence of symptoms more consistent with infection (fever, chills, fatigue, malaise)

## Signs

- Clinical presentation may be highly variable ranging from no overt physical signs to evidence of acute allergic reaction.
- Signs of infection such as elevated temperature, abdominal pain, or visibly bloody diarrhea should prompt investigation of alternative explanations prior to diagnosing medication-related diarrhea.



## CLOSTRIDIUM DIFFICILE

*C. difficile* is responsible for significant disease burden associated primarily with colitis and diarrhea in hospitalized patients and in those receiving (or recently received) antibiotics. Physicians should have a high index of suspicion for *C. difficile* in any patient who presents with diarrhea in these circumstances.

- Gram-positive spore-forming rod
- Associated with approximately 3 million cases of diarrhea and/or colitis annually in the United States
- Mortality associated with *C. difficile* infection is 1% to 2.5%.
- Hospitalization and antibiotic use is the most common precedent risk factor.
- Prevalence is rising among population with no precedent risk factors (18:100,000 in 2004).
- Antibiotics classically associated with *C. difficile* colitis include clindamycin, broad-spectrum penicillins and cephalosporins.
- High risk of colitis is also associated with hospital contact with infected individuals; 13% of all hospitalized patients acquire *C. difficile* by 2 weeks; 50% do so by 1 month. Time to acquisition is 18.9 days if not in the same room with an infected patient; it is 3.2 days when in the same room with an infected patient.
- Treatment consists of discontinuation of the inciting antibiotic whenever possible.
- First-line therapy for *C. difficile* diarrhea is metronidazole 500 mg PO three or four times a day for 10 to 14 days.
- Second line therapy consists of vancomycin 125 to 500 mg PO every 6 hours for 10 to 14 days.

## Comments and Treatment Considerations

When a diagnosis of medication-related diarrhea is made the physician is faced with the challenge of weighing the necessity of the medication against the severity of the disease. When the medication is easily replaced and/or the symptoms are severe, consideration should be given to discontinuing the medication and replacing it with an alternative. When the medication is not easily replaced and/or the

symptoms are mild, adjustments in dose may be sufficient to ameliorate the diarrhea.

Short-term medications can often be continued while the patient is treated symptomatically for the GI complaints. Diarrhea that presents shortly after the use of antibiotics or hospitalization should prompt consideration of *C. difficile* with appropriate stool studies and treatment as indicated. Treatment of *C. difficile* consists of either metronidazole 500 mg PO three or four times a day for 10 to 14 days or vancomycin 125 to 500 mg PO every 6 hours for 10 to 14 days.

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